

Research Institute—Poison Control Centers: Is There an Antidote for Budget Cuts?), 103rd Cong, 2d Sess, 1994

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## Whither Sarcoidosis?

*We dance around in a ring and suppose,  
But the Secret sits in the middle and knows*

"Secret Sits"  
ROBERT FROST

DURING THE LAST QUARTER of the 19th century, Jonathan Hutchinson was one of the best-known medical consultants in London. An astute clinical observer, he was an outstanding combination of surgeon, dermatologist, ophthalmologist, syphilologist, internist, and expert on leprosy. In 1877, in his *Illustrations of Clinical Surgery*, he described the case of a 58-year-old man with large, purple, scaly, irregular, nontender skin lesions, arthritis, and chronic renal disease. Most medical historians believe that Hutchinson's patient suffered from what we now call sarcoidosis.<sup>1</sup>

Now, more than a century after Hutchinson's first description, sarcoidosis has emerged as a multisystem disorder characterized by the presence of noncaseating granulomata in the affected organs. Sarcoidosis has a high prevalence rate in Scandinavian countries, England, Ireland, North America, and Japan, but it is less frequent in Central and South America, mainland China, and Africa.<sup>2</sup> Despite the worldwide occurrence of sarcoidosis, the cause of the disease remains obscure and the understanding of its pathogenesis confounding and controversial. Attempts to elucidate its cause have been disappointingly thwarted by the lack of an animal model and the failure to identify the antigen. For practicing clinicians, the current status of knowledge of sarcoidosis has been reviewed by Asha N. Chesnutt, MD, in this issue of the *Journal*.<sup>3</sup>

The histopathologic hallmark of sarcoidosis is a well-defined round or oval granuloma made up of compact, radially arranged epithelioid cells with pale-staining nuclei. Lymphocytes may be found within the granuloma, but they are usually seen at the periphery.<sup>4</sup> The giant cell of the sarcoid granuloma is of the Langhans type in which the nuclei are arranged in an arc or a circular pattern around a central granular zone. Caseation is absent, but minor degrees of fibrinoid necrosis may be seen, particularly in larger granulomas. Asteroid, Schaumann's, and Hamazaki-Wesenberg bodies are inclusion bodies frequently found within the epithelioid and giant cells; none of the inclusion bodies are, however, specific for sarcoidosis. The structure of the granuloma is an example of a perimeter defense commonly seen in many infectious and noninfectious disorders caused by various bacterial, fungal, viral, protozoan, parasitic, and mineral antigens. On the other hand, in sarcoid granulomas, no identifiable agent has ever been convincingly demonstrated.

Although the nature of the alien agent that causes noncaseating granuloma remains hidden, sophisticated

immunologic, molecular biologic, and bronchoalveolar lavage techniques have given us a road map of the events that lead to granuloma formation. Sarcoid granuloma in the lungs appears to be an exaggerated immune response to an inhaled agent of low solubility and degradability.<sup>5</sup> The first step in the pathogenesis of sarcoidosis is the presentation of an unknown antigen(s) by macrophages bearing increased expression of major histocompatibility class II molecules to T cells of Th 1 type. This results in T-cell proliferation and activation. These activated T cells release a number of cytokines, including interleukin-2, monocyte chemotactic factors, macrophage migration inhibition factor, and leukocyte inhibitory factor.<sup>6</sup> Interleukin-2 activates and expands various clones of T lymphocytes, causing alveolitis. The monocyte chemotactic factor attracts monocytes from blood into the lungs. Other mediators such as macrophage migration inhibitory factor influence the trapped monocytes that are ready to transform into epithelial cells and modulate the formation of a granuloma. The granuloma formation and associated helper (CD4<sup>+</sup>) T-lymphocyte alveolitis may lead to substantial alveolar injury. At this time, when the lung is the site of a tremendous outpouring of lymphocytes, the peripheral circulation shows a CD4<sup>+</sup> T-cell lymphopenia resulting in the depression of cutaneous delayed-hypersensitivity reactions.

Why does granuloma formation spontaneously subside in most patients, whereas in a few it progresses to fibrosis? Perhaps the two processes are not closely related. There is some evidence, however, that interferon gamma produced by Th 1 lymphocytes causes an increase in platelet-derived growth factor containing  $\beta$  subunits (PDGF- $\beta$ ) from macrophages.<sup>7</sup> Platelet-derived growth factor- $\beta$  is chemotactic and a potent stimulant for fibroblasts, the main effector cell in the fibrotic response. Other cytokines that are chemoattractants for fibroblasts include transforming growth factor- $\beta$  and matrix proteins. The mechanisms accounting for the increased production of matrix proteins—laminin, fibronectin, collagen peptides, elastin-derived peptides—are unknown.

We come back to the central question: What instigates the granuloma formation? From time to time we have incriminated *Mycobacterium tuberculosis* and atypical mycobacteria, but without much success.<sup>8</sup> Recently investigators demonstrated an increase in  $\gamma$ - $\delta$  cells in blood and lungs in sarcoidosis.<sup>9</sup> The T cells that bear  $\gamma$ - $\delta$  receptors are also prominent in leprosy, leishmaniasis, mycobacterial proteins, and heat-shock proteins. They suggested that one of these factors initiated the immune response that expanded into multisystem sarcoidosis.<sup>9</sup> Following the lead, many other investigators have used the polymerase chain reaction to detect mycobacterial DNA in clinical specimens from patients with sarcoidosis. *Mycobacterium tuberculosis* DNA was found in half of the sarcoidosis patients.<sup>10</sup> The findings are being hotly contested by other groups who did not find any mycobacterial DNA in bronchoalveolar lavage or tissue cells in sarcoidosis.

Many years ago it was suggested that sarcoidosis was caused by a transmissible agent.<sup>11,12(p20)</sup> Recently disseminated granulomatous inflammation developed in two patients without sarcoidosis who received heart transplants from donors who had sarcoidosis.<sup>13</sup> Granulomas have also occurred in heart and lung allografts in patients with sarcoidosis who received heart and lungs from nonsarcoidotic donors. These observations raise the possibility of a transmissible causative agent. Furthermore, the agent(s) remaining sequestered in the body is able to withstand aggressive immunosuppression and is capable of attacking transplanted lungs that have normal ventilation and perfusion.<sup>14</sup> If, indeed, there is a transmissible agent, where does it reside? Interestingly, a group of patients with sarcoidosis who had liver transplants for sarcoidosis or other causes of liver disease showed regression of the multisystem disease.<sup>15</sup> Did sarcoidosis subside in these patients because of immunosuppression or because of the removal of the diseased liver, the storehouse of the causative agent?

It is widely accepted that there is a sarcoid diathesis or constitution, but no definite genetic factors relating to the cause have so far been detected. The disease is clearly a worldwide phenomenon. Numerous contributing factors, including occupation, hobbies, pets, alcohol, tobacco, place of residence, family history, and use of drugs, have been analyzed, but no relationship has been found. It is relevant that the disease mostly affects persons between 20 and 50 years in age. Are these mobile, healthy, working people at a constant risk of inhaling an agent that is present universally? Is there another unidentified virus lurking around? The search continues.<sup>16</sup>

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## Portal Hypertension— The Surgical Pendulum

THE PENDULUM HAS SWUNG to and fro as to the role of surgical management for portal hypertension since Nicolai Eck first advocated his portacaval fistula. Eck's justification to use this shunt in humans was based on an 87% mortality in dogs. His bravado was rapidly countered by Pavlov's systematic assessment of the risks of liver failure with the deprivation of portal venous flow to the liver. A flurry of surgical activity in the early 20th century was characterized by Vidal's "forced" shunt and attempts at partial decompression by Morison's omentopexy.<sup>1</sup> Poor results led to abandoning the use of surgical therapy until the 1940s when a group at Columbia-Presbyterian Medical Center (New York, NY) popularized total portal systemic shunting. Initial enthusiasm, based on excellent control of variceal bleeding, soon waned when randomized trials documented the side effects of total portal diversion.<sup>1</sup> Surgeons sought a better way to manage variceal bleeding by selective variceal decompression<sup>2</sup> and extensive devascularization procedures<sup>3</sup> in the 1970s. Although popularity for these operations largely disappeared in the 1980s under the acclaim of sclerotherapy, by the late 1980s and 1990s, liver transplantation has swung the pendulum once more towards surgical therapy for some patients.<sup>4</sup> In addition, the realities of bleeding through sclerotherapy have brought back some of the previous surgical approaches in good-risk patients who do not need transplantation.

In their excellent review of surgical options in the management of portal hypertension in this issue of the journal, Collins and Sarfeh carefully outline the goals and outcomes of the various surgical possibilities.<sup>5</sup> How does a physician really decide what to do with a patient who presents with variceal bleeding? Clearly, variceal bleeding is one of those sentinel events in medical practice that requires full evaluation and definitive management decisions. Let us examine this question in a little more detail.

### Acute Variceal Bleeding

Acute variceal bleeding is currently managed by endoscopic sclerotherapy. A new challenger, however, somatostatin or its analogue octreotide, is gaining popularity, with two randomized trials in acute bleeding documenting equal efficacy to sclerotherapy.<sup>6,7</sup> To practitioners who see few patients with variceal bleeding and who do sclerotherapy only occasionally, these data support the